

REMARKS

The Pending Claims:

Claims 1-16 are pending and under active consideration.

The Office Action:

Claims 1-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Green et al. (U.S. Patent No. 5,780,601) in view of Nicholson et al. (U.S. Patent No. 5,681,936).

The Amendment:

No claims are currently amended.

Rejection under 35 U.S.C. § 103(a)

Claims 1-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Green et al. (U.S. Patent No. 5,780,601) in view of Nicholson et al. (U.S. Patent No. 5,681,936).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In the previous response submitted on October 11, 2007, Applicants explained why the combination of Green and Nicholson does not teach or suggest lysis of bacteria or bacterial host cells in a fermentation broth, a limitation present in the pending claims.

In response, the Examiner states on Pages 5-6 of the present Office Action that:

The Examiner disagrees with Applicant's assertion that the combination of references do not teach lysing bacteria or bacterial host cells in a fermentation broth followed by diafiltration of the lysed fermentation broth. It should be noted that Green et al. teach that an alternative source culture medium (fermentation broth) of *H. influenza* cells (bacterial cells) can be used (column 4, paragraph 4). As stated above, it is the combination of references that teach the claimed invention. *Emphasis added.*

The fact that Green and Nicholson allegedly describe a lysis step and a fermentation broth, does not suggest the lysis of cells in a fermentation broth, as claimed. Green describes the use of "an alternative source of outer membrane components..." as provided in Loeb, M. R. (1987) *Infection and Immunity* 55(11):2612-2618. At column 4, paragraph 4. In Loeb, cells are purified and removed from the fermentation broth before a lysis step occurs (See Loeb *et al.* "The cells and medium were concentrated to 400 ml by a Pellicon apparatus...cells and supernatant fluid were obtained as separate fractions...The cells were suspended in [ ] Tris hydrochloride, pH 7.8, and centrifuged as above to yield a supernatant rich in outer membrane... Each preparation was suspended with a homogenizer...[and then] a nonionic detergent, octylpolyoxyethylene (OPOE), was added." At Page 2613, column 1, lines 1-30.).

Therefore, contrary to the Examiner's assertion, cell lysis in a fermentation broth, as claimed, does not occur in Green or Loeb.

The initial centrifugation steps (as taught in Green), allows for cells containing the target protein to be separated from particulate present in a fermentation broth. Subsequent lysis of the cells releases proteins into a clarified solution free from potentially contaminating particulate. There is nothing in Green or Nicholson to suggest a modification in the timing of cell lysis such that proteins present in the cells are released into a non-clarified, fermentation broth containing potentially contaminating particulate. Both descriptions teach away, not toward this modification. In fact, Nicholson describes a methodology intended to keep cells intact and avoid lysis altogether.

By lysing the bacterial cells in a fermentation broth, Applicants were able to combine the clarification and extraction processes into one unit operation without the need for centrifugation and multiple units, including columns and resuspensions. Efficient extraction of inner-membrane proteins by the claimed process was a result evident only after the invention described in the present application.

The Examiner concludes that "[i]n view of all the above, there is nothing on the record to suggest that the combination of reference [sic] does not teach the claimed invention." Page 6, 2<sup>nd</sup> paragraph. It is the Examiner's duty to establish a *prima facie* case of obviousness, not Applicant's duty to show nonobviousness, as this conclusion seems to imply. See MPEP § 2142. Since the examiner has not produced a *prima facie* case of obviousness, Applicants are under no obligation to submit evidence of nonobviousness.

Nonetheless, Applicants have provided overwhelming evidence to suggest that the combination of references do not teach the claimed invention. Accordingly, withdrawal of the rejection of claims 1-16 under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the application is in condition for allowance. However, the Examiner is invited to contact undersigned if any outstanding issues remain.

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